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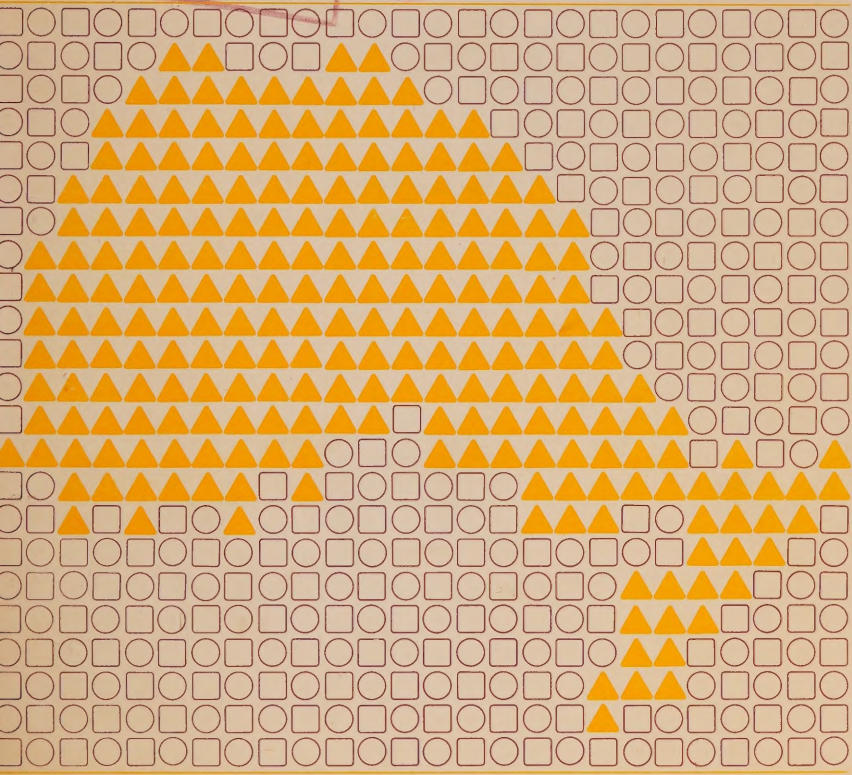
Occupational Health in Ontario

Volume 1, Number 4 October, 1980

Occupational Exposure to Silica

Carcinogenesis — Interpreting Test Results

The Importance of Worker Compliance in The Use of Hearing Protectors



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Occupational Health in Ontario

Volume 1, Number 4 October, 1980

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Examples

1. Lee WR, and Miles S. Postgraduate preparation for occupational medicine. *J. Soc. Occup. Med.* 1976; 26:115-119.
2. Department of Health and Social Security. Notes on the diagnoses of occupational diseases, rev ed 1972; London HMSO.
3. Gamble JF, and Battigelli MC. Epidemiology. In: Clayton GD and Clayton FE. eds *Patty's industrial hygiene and toxicology*. New York: McGraw Hill, 1978: Vol 1; 113-116.

Two copies of both the manuscript and illustrations should be sent to:
The Editor
Occupational Health in Ontario
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400 University Ave.
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Correspondence

To the Editor:

I would like to comment on the article written by Murray Finkelstein on his review of aluminum prophylaxis against silacosis (*sic*) in the April issue of *Occupational Health in Ontario*. As an introduction, Mr. Lloyd Tataryn, author of "Dying for a Living" and I collaborated to "spark" the controversy in the media last fall.[2]

Dr. Finkelstein reported "Inhalation experiments in animals have failed to find any evidence for aluminum induced lung fibrosis. Aluminum appears to act as a nuisance dust stimulating an outpouring of scavenger cells." On the contrary it has been shown that intratracheal injection of large doses of aluminum powders causes pulmonary fibrosis in rats[3] and that some types of aluminum may produce a fibrosis as severe as can be produced by quartz.[4] If Dr. Finkelstein would have consulted Tataryn's book carefully, he would have noted a reference to Zaida (*sic*) who devotes eight pages to pneumoconiosis caused by aluminum.[5]

Another significant deficiency in Finkelstein's review was that he failed to give any details of why the aluminum prophylaxic theory was discarded in Great Britain[6] and rejected by the Government of South Africa.[7]

Besides the issue of scientific debate of the use of prophylaxis, Tataryn's book revealed that there was also a moral issue. The McIntyre Aluminum Foundation stated before the Royal Commission on the Health and Safety in Ontario Mines "that metallic aluminum powder when properly administered will prevent silacosis in experimental animal (*sic*) is now universally accepted."[8] The fact is that the Foundation was fully aware of the work by Dr. Ian Webster of

References

1. Finkelstein, M. A review of aluminum prophylaxis against silicosis. *Occup. Health in Ont.* Vol. 1 (2) 22-26.

2. Tataryn, L. *Dying for a Living*. Deneau and Greenberg Ltd. Toronto (1979).

3. Gross P, Harley RA, de Treville RTP. Pulmonary reaction to metallic aluminum powders. *Arch. Environ. Health*. Vol. 26, 227-236 (1973).

4. King EJ, Harrison CV, Mohanty CP, and Nagelsmidt G. The effects of various forms of alumina on the lungs of rats. *J. Path. Bact.* Vol. 75, 429-434 (1958).

South Africa who concluded that McIntyre Aluminum powder did not prevent silacosis.[7]

Apart from the above, the review was adequate for the purpose of a government task force.

R.A. Phaneuf
3775 University St.,
Montréal, PQ, H3A 2B4

The above letter was referred to Dr. Finkelstein, who offers the following reply:

To the Editor:

My review of aluminum prophylaxis is based upon a study of published literature. Although, we did computerized literature searches, we were unable to find any publication which indicated why prophylaxis was not adopted by Britain or South Africa. We were unable to locate a copy of Dr. Webster's paper in Canada and though he promised to send us a copy, we never received one.

In reading Mr. Phaneuf's letter, I find that he has a poor understanding of technical terminology. This probably explains his misinterpretation of "inhalation" as being equivalent to "intratracheal injection". An inhalation experiment is obviously a much more physiological situation than the injection of large quantities of dust into the trachea, and none of the well-performed, published inhalation studies has revealed fibrosis from inhaled aluminum powder.

Similarly, Mr. Phaneuf fails to understand the difference between prophylaxis and therapy of established disease. The paper by Kennedy (reference 6) is a study of the use of aluminum for the treatment of established silicosis. There is, of course, no indication that aluminum inhalations are at all useful for therapy.

Finally, I am not sure whether or not I should be insulted by his last statement. Perhaps Mr. Phaneuf could elaborate.

5. Zaida SH. *Experimental Pneumoconiosis*. The Johns Hopkins Press, Baltimore, p. 325 (1969).

6. Kennedy MCS. Aluminum powder inhalations in the treatment of silicosis of pottery workers and pneumoconiosis of coal miners. *Br. J. Ind. Med.* Vol. 13, 85-101 (1956).

7. Webster Ian. Prevention of silicosis: aluminum prophylaxis. *South African Pneumoconiosis Review*, p. 11 (1968).

8. Dix WB. *Brief to the Royal Commission on Health and Safety of Workers in Ontario Mines*. p. 12 (1975).

Joan C. McEwan,
MB, ChB, DPH

Occupational Exposure to Silica

Summary

In North America, studies of the granite industry provide the most detailed epidemiological information available on persons exposed to quartz. This paper therefore concentrates on the effect of silica in this industry, while providing an overview of studies of other industries on this continent where the potential for silicosis exists.

In industries where there is exposure to tridymite, crystobalite and silica flour the likelihood of an increase in toxicity over that of quartz must be considered.

Silica (SiO_2) exists in the following forms:

Crystalline Silica

Quartz – hexagonal crystals
Cristobalite – cubic crystals
Tridymite – hexagonal crystals
Coesite – a high temperature, high pressure form
Stishovite – octahedral crystals – a rare form.
Silica Flour – a ground quartz in which 70 per cent. of the particles are below 5μm, with a high percentage less than 0.5 μm.

Amorphous Silica

Sublimed crystalline silica and quartz glass
Diatomite or diatomaceous earth.

Occupations in which exposure to silica exists include quarrying, pottery making, brickmaking (particularly in the manufacturing of refractory bricks), foundry working, gold, tin, copper, mica and other metal mining and mine drilling, offshore drilling, stone cutting and grinding, shotblasting, sandblasting, sand pulverizing, tunnelling, lens grinding, asbestos cement manufacture, manufacture of abrasives, boiler scaling and vitreous enamelling.

Mode of Action

The primary site of action is the alveolar macrophage, on which certain forms of silica exert their cytotoxic effect.

The particle is engulfed, with creation of a phagosome from invagination of the cell membrane. The phagosomal membrane ruptures, apparently due to the reaction between silicic acid, a powerful hydrogen bonding agent found on the surface of certain crystalline forms of silica, and the phosphate ester groups of phospholipids in the cell membrane. After disruption, lysosomal enzymes are released and the macrophage dies. The silica particle is released to exert its toxic

action again. (Stishovite, though crystalline, lacks cytotoxic properties and this may be due to the octahedral crystal structure preventing the orientation of silanol groups and their saturation to form silicic acid).

Particles engulfed in the macrophage may either move towards the terminal bronchioles and thence to the muco-ciliary escalator, or migrate from the alveoli to the interstitial pulmonary tissue and thence, in the lymphatic system, towards the bronchial lymph nodes. The fibrogenic reaction of silica may be seen near respiratory bronchioles as well as in the lymph nodes.

The mechanism of the formation of the silicotic nodule is still uncertain and remains the subject of intensive research. Proliferation of fibroblasts leads to the formation of fibrohyaline bundles of collagen with an acellular homogeneous centre surrounded by concentric rings of cells. This halo of cells is of varying thickness, probably depending on the age of the nodule, and consists of macrophages and plasma cells. Quartz particles can be demonstrated in the central zone and around the periphery of the nodules but are absent from the cellular capsule.

The diagnosis of silicosis rests on the radiographic changes and history of occupational exposure to dusts having a high free silica content.

Generally, the changes which are seen in Ontario are the result of inhaling pure silica dust containing a high proportion of free silica. The relevant particle sizes are 0.5 to 5 μm, with the most fibrogenic size considered to be 1 μm. Smaller particles than 0.5 μm tend to be exhaled, while larger sizes do not reach the alveoli. The diagnosis would not be made in the absence of silicotic nodules unless the disease appeared in acute form.

The typical radiographic appearance in the early stages of the disease is of nodulation in the upper lung fields. This selective regional deposition is considered to be related to the angles and diameter of the bronchi, their length and number of branches. In particular there is a less acute angulation of the main right upper lung bronchus.

Initially the nodules are small (usually 1 to 3 mm) and discrete. As the disease progresses, they increase in number and size and also occupy the lower lung fields.

Conglomeration of nodules may follow and may be visible as large and irregular masses with surrounding

bullae. Increasing fibrosis, or ischemic or infective changes, may bring about a release of silica from the nodules into an adjacent air space, allowing fresh nodules to form or the nodules to increase in size. Changes in the radiographic appearance are characteristically gradual.

Most symptoms are related to complications of simple silicosis such as bronchitis and emphysema. An unproductive cough may develop unless purulent sputum arises from a bronchial infection. Breathlessness develops gradually and there may be a slight restrictive ventilatory effect. A late effect may be the development of cor pulmonale.

With increasing nodulation there may be shrinkage of the upper lung lobes with a compensatory emphysema in the lower lung fields.

When there is very heavy exposure to free silica, fibrosis may be massive and occur within five to 15 years or even less.

After intense exposure of short duration to dusts of high quartz content and small particle size, such as in sandblasting or abrasives manufacturing, an 'acute' silicosis may occur, characterized by an outpouring of fluid into the alveoli, leading to an alveolar proteinosis. If the patient survives this acute phase of the illness, nodule formation is immature and the chest x-ray shows an interstitial fibrosis of varying degree, giving a hazy appearance in the lower lung fields.

In earlier years, silicotics succumbed to tuberculous infection, particularly when the silicosis was in an advanced stage. With the lessening incidence of tuberculosis in the general population, silico-tuberculosis is a very uncommon finding.

Exposure to Quartz

Epidemiological data sufficiently comprehensive and detailed to form the basis for a standard are limited mainly to one specific industry on this continent: the granite industry in Vermont. Considerable detail is available from a wide range of other industries, but in many of these the information is found to be lacking in one important respect: surveys of prevalence of silicosis are accompanied only by *current* measurements and analysis of dust. The length of time necessary for the disease to become evident by radiological

examination, which is the most useful comparative measurement in such studies*, means that current environmental data can only be used, if practicable at all, by extrapolation back in time. For any earlier estimates of dust levels to be made, the conditions in each industry and the use made of protective devices are only two of the important variables to be considered.

Analysis of a range of studies is made in the document recommending a standard for occupational exposure to crystalline silica published in the United States by the National Institute for Occupational Safety and Health in 1974.

Granite Industry

This industry has been located in Barre, Vermont, for over 150 years and has a stable work force, enabling valuable epidemiological studies to be done.

Russell in 1941[2] summarized studies undertaken in 1924 and in 1937-38, and presented new data. He stated that in this industry there were reactions to the dust hazard in direct proportion to the intensity of dustiness.

The introduction of pneumatic tools in the industry around 1900 led to a dramatic rise in the death rate of these workers. Deaths from tuberculosis rose from a crude rate of 1.5 per 1,000 in 1890 to 19.5 per 1,000 by 1926 in Barre granite cutters, while in general in the New England rural male population, mortality from this cause fell slightly during this period. It is stated by Russell that while there was probably a greater amount of dustiness in the general plant atmosphere from the time these tools were introduced in about the year 1900, the measurements taken near the source of the dust probably had not changed much in 40 years, as ventilating devices were not introduced until shortly before his 1941 report. However, no measure-

**The Appendix* summarizes the methods used in various studies for interpretation of chest x-rays.

ments were given for the years prior to his studies. In 1941, he re-examined as many as possible of the workers examined in 1924-26. Information was available on 118 of these. The workers were divided into groups according to dust exposure:

Group A – hand-pneumatic-tool cutters exposed to about 60 mppcf dust.

Group B – surface machine operators and cutters exposed to more than the average dustiness of the plants, which was about 44 mppcf for operators of surface cutting machines, 37 mppcf for carvers and letterers and 27 mppcf for tool grinders (wet dust).

Group C – in occupations exposed to the average dustiness of the plants, about 20 mppcf, and

Group D – in occupations exposed to less than the average dustiness of the plants. Average exposure was approximately 6 mppcf.

Office workers were exposed to about 2 mppcf.

In reporting the cases of silicosis from this group, Russell gave the following results:

Groups A-B

a) those who continued in former occupations and
b) those who moved to less dusty occupations.

Silicosis progressed in both groups, and the likelihood of tuberculosis complication did not lessen for Group B.

Groups C-D

In 33 men employed in these groups there were slight changes from early to later forms of fibrosis and silicosis. The number of men in each group is not given. The report states that there were two cases of early silicosis in Group C but none in Group D. Neither physical examination nor silicosis records in Group D showed any indication of unfavourable health effects.

Russell concluded that for Groups A and B the effects of dust were definitely harmful. For Group C, with an average exposure of 20 mppcf there was some question as to harmful effect, but for Group D, with an average exposure of 6 mppcf and a limit of 9 mppcf, no harmful effect was found.

Hosey, Trasko and Ashe published a further report in 1955, and although direct comparisons cannot be made with the report by Russell, the findings are supportive.[3] Of men whose chest x-rays showed changes to definite silicosis between 1937 and 1955, 32 entered the industry before 1920, 113 between 1920 and 1929 and eight after 1930 but before 1937. One man starting work since 1937 had 'questionable' silicosis. He was 74 years of age in 1954 and had been a maintenance worker in a shed with no obvious silica dust exposure. One operation in the industry at this time (final polishing) had a dust count averaging over 10 mppcf and in most areas the counts averaged less than 5 mppcf.

In 1964, Ashe and Bergstrom published a report on workers in the granite manufacturing industry after 26 years of dust control (from the time when dust control equipment was introduced which was between 1937 and 1940).[4] In 1963, over 98 per cent of the labour force of about 1,700 had been x-rayed at least once.

Prior to dust control, 379 men out of 987 men x-rayed (38.4 per cent) had silicosis. This is represented graphically in Figure I and II for granite cutters and for men in other occupations in granite working. No silicosis developed in men with less than five years of exposure, but the percentage of silicotics rose at a steady rate thereafter. The average dust levels are given in the report as 40 to 60 mppcf for granite cutters and 20 mppcf for non-granite cutters (estimated from general air levels in 1927).

For the men with higher exposure (granite cutters), Figure I illustrates that silicosis is likely to occur, given sufficient time, and for other workers in granite (Figure II), the percentage of men developing silicosis will rise to over 50 after 30 years.

Contrasting with the amount of silicosis in workers exployed prior to dust control, no cases of silicosis were found among 885 granite shed workers employed and x-rayed in 1963 whose work exposure was limited to the dust control period. The number of men in this category who had worked for 20 or more years was 118. The highest dust level reported after the institution of controls was 12 mppcf for cutters and 6 mppcf for those exposed to general air, and it seems likely, judging from levels reported in 1955, that this might be an over-estimation of the levels of exposure for most of these men. The dustiness, since 1937, was considered to average 5 mppcf.

Expressed in terms of mass, according to a review by Ayer[5] of the work by Sutton and Reno, 10 mppcf dust would be equivalent to a value of 0.1 mg/m^3 quartz in the respirable fraction of dust in the granite industry, after dust control, therefore 5 mppcf = 0.05 mg/m^3 quartz.

Further studies on the granite workers were undertaken by Theriault and co-workers. One of these concerned the development of an Exposure Index and its relation to Forced Vital Capacity as a dependent variable.[6]

Exposure to dust levels in 1972 was estimated by personal mass respirable dust samplers. In this study, the quartz content of the dust, estimated by infra-red photometry, was 9 per cent.

Multiple regression analysis was applied to age, height, smoking history, dust, exposure (in years) and ventilatory function. Occupational classification and mass respirable granite dust concentration were used to develop one matrix and occupational classification and mass respirable quartz in micrograms per cubic metre were used to develop another.

From these data and individual occupational histories, exposure indices were developed based on lifetime exposure estimates.

The index which correlated most highly with changes in Vital Capacity was that related to granite dust concentration and was called the Dust Year.*

Decrease in Forced Vital Capacity and FEV_1 was estimated at 2 mL per dust-year. No quantitative conclusions can be drawn with respect to silicosis so this study is not discussed further in detail.

The second study in this series[7] related to pulmonary function tests administered in 792 granite workers at the time of their annual chest x-ray. Smoking histories were also obtained on this group. Using the individual lifetime exposure estimates already prepared, multiple regression analyses were performed to separate the effect of dust. Three sets of controls were used for the study (granite workers with no dust exposure, 'normal' values from other studies, and marble workers not exposed to granite dust) and it was determined that there is an average decrease in Forced Vital Capacity of 2 mL/year for a worker exposed to the average dust concentration in the granite sheds, when compared with these three control groups.

In the third study in the same series,[8] chest x-rays were classified and studied in relation to dust, pulmonary function and smoking. A delay of some years was demonstrated between alterations in pulmonary function and observed changes in chest x-rays. While it is concluded that early detection of dust effects in groups of workers would be better achieved by pulmonary function tests than by roentgenograms, the significance of this would be difficult to evaluate in any individual case.

In 1974 the National Institute for Occupational Safety and Health recommended that no worker should be exposed to a time-weighted average concentration of free silica greater than 50 micrograms per cubic metre of air as determined by a full-shift sample for up to a 10-hour work day, 40 hour work week,[9] principally on the information relating to granite workers, and particularly on the epidemiological studies of Russell, and Ashe and Bergstrom. This recommendation has not so far been implemented.

**Dust year* – Expressed for each employee by the formula $\sum_{1}^{N}(K_j x T_j)$ where T_j = number of years employee was at jth workplace, K_j = concentration of mass respirable granite dust at jth workplace and n = the number of workplaces. This lifetime exposure was divided by the average dust exposure of the population to obtain the "dust year".

A similar calculation was used to express a 'quartz-year', using mass respirable quartz instead of mass respirable granite dust.

Metal Mines

Included among U.S. studies is a survey of metal mines by Flinn *et al*[10] and a survey of foundries by Renes *et al*.[11] These surveys show the prevalence of silicosis at the time they were done. Dust counts in earlier years are not available in these reports.

In U.S. metal mines principally extracting lead-copper or lead-silver ores, 20,500 persons were studied (14,000 underground) between 1958 and 1960, representing over 50 per cent of the working population of such mines in the United States at that time. There were 14,480 samples collected by impinger underground and 789 full-shift average exposures determined. Of these, 13.2 per cent exceeded the 1962 ACGIH Threshold Limit Value of $\frac{250}{\%SiO_2 + 5}$ mppcf. Distribution of weighted averages exceeding the Threshold Limit Value was not uniform in the mines studied. A few mines contributed most of this excess exposure. The amount of free silica in settled dust ranged from 2 to 95 per cent (over 50 per cent in 6 per cent of the mines).

Responses to a program of chest x-rays of workers employed at the time varied from 50 to 100 per cent, the average being 77 per cent for the 50 non-uranium mines included, and in 14,076 chest x-rays 3.4 per cen were classified as consistent with silicosis. This percentage varied greatly from mine to mine as did the proportion of simple silicosis to complicated silicosis, which was overall roughly 2:1. It is not possible to state from the study whether or not the miners showing silicosis came from those mines where the percentage of free silica was high. This very high proportion of complicated silicosis probably reflects the world-wide epidemiological situation in tuberculosis at that time and immediately after World War 2: this diagnosis in general was confined to older men with more than 15 years of metal mining experience. No silicosis was observed in workers with less than five years of exposure. The proportion of men with silicosis in relation to years of exposure for four occupational groups, taking 25 per cent as the average calculation of free silica, is shown in Figure III.

Foundries

In Illinois in 1948-49, 18 foundries employing 1937 workers were studied.[1]

The silica content of the respirable dust was estimated at between 13 and 19 per cent, with 30 per cent free silica in settled dust. Eleven hundred samples of airborne dust were taken by standard impinger. Eighty-two per cent of samples gave results below 6.9 mppcf, and 4 per cent were above 31 mppcf.

Chest x-rays taken at the time of the study on 1824 men out of a possible number of 1937, showed that in 9.2 per cent significant pulmonary fibrosis of occupational origin was present (this included 'ground glass 2' and all nodular stages of silicosis), and for employees who had worked for more than 20 years in the industry the prevalence was 26 per cent, with casting cleaners most affected. Figure IV shows the relationship between years of exposure and the proportion of gray iron foundrymen and steel foundrymen with silicosis.

The authors noted a tendency for workers to develop a 'ground glass 2' level of fibrosis earlier but there was less progression of nodular silicosis than in U.S. coal miners and metal miners.

Brick Industry

Rajhans and Budlovsky in 1972 reported on dust conditions in brick plants in Ontario.[12] Midget impingers were used to determine particle concentrations, and a Hexhlet sampler to obtain respirable mass measurements. The percentage of free silica at different plants varied between 7.5 and 21 in the respirable dust. The percentage of free silica in the raw material was somewhat similar to that in the study in Britain by Keatinge and Potter in 1949 (22 to 32 per cent).[13]

The Threshold Limit Value was exceeded by both methods of analysis by a considerable margin: from impinger counts 8-114 times the Threshold Limit Value and from Hexhlet counts 1.27 to 7.1 times the Threshold Limit Value. Chest x-rays were taken of 1,084 current employees (out of a possible total of 1,166 persons) of eight brick and two tile plants and divided into two groups: one of men working in the crushing and grinding areas, and the other of men in the less dusty environments. No cases of silicosis were found, although a higher percentage of employees in crushers showed dust effects. An analysis of years of exposure in relation to the x-ray findings is not made, but the authors state that a relationship was sought; in some plants there was exposure for 15, 16, 18 and 30 years in some employees, while for others

exposure could have been limited to the period of employment prior to x-ray. The periodic chest x-ray program took place every 18 months. Individual dust exposures were difficult to determine because seniority entailed movement and supervision in different areas of the plant. Keatinge and Potter also reported similar findings.[13]

A categorical statement that silicosis is not associated with employment in brick plants cannot be made on the basis of these studies, but it appears that short exposure is unlikely to produce cases, even where there is significant exposure to respirable dust containing free silica.

The authors suggest several interesting hypotheses to explain the lack of an association between exposure and cases of silicosis and it may be that as they suggest, the present ACGIH TLVs for dust are not applicable to the brick industry.

Pottery Industry

Flinn and colleagues of the U.S. Public Health Service reported in 1939 on the relationship of dust in the pottery industry to silicosis, the results of a study in 1936 to 1937 of nine potteries in West Virginia.[14] Of 2,516 employees, 64 were excluded from most of the calculations because of previous exposure to coal mining or quarrying.

The dust exposure of individual exployees was calculated by multiplying average dust exposure in each job by the number of years in that job and dividing the total dust count by total years employed. The composition of the dust varied in different departments. In general where dust counts were high, quartz content was also high and the reverse was also true. The quartz content varied from 1 to 39 per cent, being highest in the clay shop and slip areas (transportation of raw materials).

Of those men exposed to an average of less than 4 mppcf of dust, two cases of early silicosis were found: one in a man who had worked for between 10 to 19 years and the other in a man who had worked for between 20 and 29 years. It was stated that reasonable doubt existed whether higher dust values might not have contributed to exposure in these instances. Additionally the particle size to which workers are exposed may be somewhat different from that found in other industries where exposure of free silica occurs: indications are that almost all particles are less than 5 μm in size.

Nevertheless, 89 workers out of 716 exposed to dust levels of 4 to 7.9 mppcf for periods of up to over 40 years had silicosis, with a relatively high proportion in long-term employment groups (for clay shop workers and jiggermen, for example, the dust exposure is less than in other areas, the rates of pay are high, and workers stay in the same job for long periods).

It is clearly indicated that 10 mppcf would be too high a value to protect against silicosis in this industry. Figure V shows the progression of silicosis with time at different levels of dust. Approximately 80 per cent of workers exposed to more than 4 mppcf developed silicosis after 40 years of exposure.

Exposure to Cristobalite and Tridymite

King *et al*[1] investigated the potential toxicity of quartz, cristobalite, tridymite and fused silica in rats by intratracheal injection of the four modifications in purified form. Tridymite was the most active in the production of silicosis, followed by cristobalite, quartz and fused silica in decreasing order. These results confirmed experiments by earlier researchers.

The lung changes in man are dissimilar to those found in other free silica exposures, lacking in hyalinized discrete nodules and showing a diffuse cellular thickening of the walls of the air spaces, produced by proliferation of dust phagocytes.

Silica Brick Industry

Dust from various operations in the silica brick industry in Pennsylvania was estimated in 1939 to contain 75 per cent or more of free silica.[15] In the burning process of refractory brick manufacture expansion of the brick occurs with change from quartzite to tridymite and cristobalite. Traces of tridymite and cristobalite were found in the dust of all green brick operations but not in the quarry or rock crushing areas. There is no significant difference between the occurrence and extent of silicosis between green brick and burned brick employees in the groups studied.

Of men with exposure to less than 10 mppcf, no silicosis was found in those with exposure of less than 2 mppcf, but silicosis was found in 14 men out of 65 with exposure of 2 to 3.9 mppcf. With employment of over 30 years 94.2 per cent of the workers developed silicosis. Figure VI shows the number of silicotics in relation to years in the industry.

Exposure to Diatomite

Cralley, Cooper and Caplan[16] reported on conditions in a California plant in 1966. A dust abatement program was in effect by 1956 and 203 men (35 per cent) of men studied earlier in 1954[17] were still working. By 1956, 79 per cent of samples of airborne dust were under 5 mppcf and 3 per cent over 20 mppcf. The median values at that time were said to be well within the ACGIH Threshold Limit Values (5 mppcf for cristobalite-containing dust and 20 mppcf for natural diatomite).

With the use of respirators at peak levels no one hired after 1953 had developed silicosis by 1963 (there were 83 men hired after 1953 who had worked for five years or more). The period of followup was therefore short.

In 1975 Cooper and Jacobson[18] reviewed the chest x-rays at this plant and found 12 persons in the current work force who had films considered positive for pneumoconiosis from diatomite. All but two were employed prior to 1953. They stated that risk of the development of pneumoconiosis appeared to be confined to those exposed to the calcined product, but frequent change of jobs and proximity to different dusts occur. Thus in a small number of men employed for 21 years, two cases of silicosis were found.

It is not possible to state that the levels to which these workers are exposed will not be associated with silicosis, even though the dust levels before the institution of controls in 1956 were said to be higher by two orders of magnitude over those after dust control.

Exposure to Silica Flour

Nelson *et al* have reported on silica flour exposures in Ontario.[19] They gave details from an earlier report by Riddell in 1965 in which an analysis was made of the records of 356 persons who had filed claims for workmen's compensation.[20] In this earlier report, six cases of silicosis were reported from the abrasive cleanser industry. The average age of these persons when silicosis was first diagnosed was 46.9 and the average exposure time was 13.3 years, both these figures being lower than for other industries mentioned. One of these cases had an exposure of 33 years, and if this case were to be omitted the average exposure would be almost 10 years.

The average age at start of exposure was 34.5 years for all these employees, which contrasts with the average age of starting for foundry workers (22.8

years), stone cutters (17.7 years), porcelain and pottery makers (22.1 years) and silica brick handlers (25.4 years) and is closer to the average age at commencement of exposure of other ceramic workers, mixers, grinders, etc. (30.4 years). Riddell states that the exposures in which casual labour was used were more severe than those in which skilled labour was employed, but no dust levels are given.

Sampling results from four plants using silica flour are given by Nelson *et al* from a total of 24 air sampling surveys: three plants had surveys over periods of 8½ years, 17½ years and 10 years, and one plant had sampling only in one year (1937). Cases of silicosis from these plants totalled nine, with the shortest exposure of four years duration and the longest of 16.

The average dust concentrations are given in mppcf and in 181 dust counts reported the mean was 3.67 mppcf with a median value of 2.7 mppcf and a range of 0.3-17.8 mppcf. Measurements were taken by Greenburg-Smith impingers.

The authors presented data on the correlation of various sampling methods, and for the particular grade of silica flour used for the comparison (98.5 per cent silica and 8 per cent of weight $<44\ \mu m$ [−325 mesh] with a median diameter of 0.9 μm) the following relationships were demonstrated:

1) 1 mppcf by Greenburg-Smith – approx. 0.11 mg/m^3 by either gravimetric method used (Casella personal gravimetric size-selecting dust sampler and Hexhlet respirable dust sampler).

2) 1 mppcf by Midget impinger – approx. 0.08 mg/m^3 by either gravimetric method used.

Unfortunately, the data available on persons with silicosis are not sufficiently documented to be sure that other earlier industrial exposures were not responsible for the development of silicosis; and thus some doubts remain about the levels and types of dust to which they were exposed earlier.

We do not have details of the lung pathology in these cases, which would have provided useful information on the degree and type of silicosis. Evidence of an acute type of silicosis without nodulation would have added weight to the concept of a rapidly-developing form.

There may be a parallel here with exposure to other types of abrasives. Shaver's Disease, with exposure to high concentrations of finely divided aluminum and silica leads to a rapidly progressive form of pneumoconiosis.

The authors state that there is no clear-cut indication that the apparently increased toxicity of silica flour is related only to its small particle size distribution. The particle size distribution is, nevertheless, the most straightforward means available to us in estimating the respirable dust and its likelihood of retention in the lung.

For silica flour in general, it is estimated that over 98 per cent of all particles are $<5\ \mu$ in size, and thus on this basis alone it might be very readily inhaled. It would seem sensible that its estimation should be by gravimetric size-selective sampling and, in this case, using the relationship of 0.11 mg/m^3 respirable mass = 1 mppcf as a basis for assessing exposure, a figure above 0.2 mg/m^3 as an average dust concentration, is obtained for the silica flour plants mentioned, where there is considerable doubt as to safe conditions for employees. Calculated acceptable exposures have been given as 0.08, 0.16, 0.07 and 0.04 mg/m^3 for the four plants studied, based on the average dust level (calculated as mg/m^3 $\times$ the lowest number of exposure years given $\div$ 30 [assuming a working life of 30 years]).

These data led the authors to propose a TLV of 0.05 mg/m^3 for silica flour. Epidemiological evidence for this is not sufficiently detailed but a considerable number of cases of silicosis have occurred in these plants at levels which are clearly unacceptable.

Ontario data on Silicosis in the Mining Industry

Silicosis death rates have been calculated by the Workmen's Compensation Board, but we have no information which relates directly to the free silica exposure of mine workers. Information is available as to type of mine and years of employment in and outside the province for persons developing silicosis.[21]

Discussion

As already stated, studies of the granite industry provide the most detailed epidemiological information on persons exposed to quartz. The work of Ashe and Bergstrom, particularly, provides data on a sizeable group of men exposed for over 20 years in whom

silicosis did not develop.[4] The dust conditions and the amount of quartz in the dust under differing conditions in this industry have been extensively studied and carefully estimated. Errors in these data are unlikely to be very great. The population studied was stable, and silicotics would be unlikely to move away from the area and be lost to the study.

From two studies of granite workers,[2,4] a 'no effect' level of the respirable silica, expressed gravimetrically, has been estimated, and the relevant data are presented in Table I. For, at most, 31 men observed in the first study (Russell) and for 11 men in the second study (Ashe and Bergstrom) this level is given as 0.12 mg/m^3. For a larger number of men (107) exposed to less than 0.06 mg/m^3 no effect was seen after exposure for 20 to 26 years (Ashe and Bergstrom). A silicotic effect was seen at a level of 0.4 mg/m^3 quartz. A safe level might therefore lie between these figures of 0.06 mg/m^3 and 0.4 mg/m^3 quartz.

The study of metal mines[10] was designed as an overview of conditions throughout the metal mining industry at one point in time: it was therefore not conducted primarily with epidemiological analysis in mind. A particular problem in the study is that the number of mines under review varied most widely in respect of type, location, size, modernity, age of employees, stability of the working population, dust conditions and quartz content of dust.

A few mines contributed a major portion of the weighted average exposures that exceeded the limit.

The medical surveillance program was conducted separately on most of the same mines as those in which there was environmental sampling, and the response to the chest x-ray program was very variable. It is not possible to relate the amount of silicosis to specific mines where the percentage of free silica was high.

A similar problem is found in the study of foundry workers, which was conducted to determine the health status of the workers in the industry in Illinois, over a one year period. It was stated in the report that environmental conditions had improved in the previous 10 to 20 years and it was likely that the observed pulmonary fibrosis was due in part to higher dust concentrations which almost certainly existed previously. It is therefore very difficult to relate the observed effect to exposure levels.

In a study of brick plant workers in Ontario, silicosis was not found despite dust counts which were in excess of the current TLV. Short exposure did not produce cases, but the study design did not allow for epidemiological review of long-term employees.

The pottery industry report gives results of the relationship of the amount of silicosis to exposure to free silica which are out of line with some other industries in which there is exposure to granite dust.

There are doubts as to the accuracy of the personal exposure of the two workers developing silicosis at exposure levels of less than 4 mppcf after a period of less than 30 years. However, a large number of cases occurred among workers exposed to an average of between 4 and 9 mppcf for their working lifetime.

Information on particle size indicates that it may be different from that occurring in other industries where there is exposure to free silica. The nature of the work, in which there is close contact between the worker and the product, may also be important. An estimation of the 'lowest effect' level as a gravimetric equivalent in respirable quartz has been made in Table I, showing that the 'lowest effect' level is less than 0.08 mg/m^3 respirable quartz. Two cases of silicosis occurred in 317 men employed for more than 10 years. This 'lowest effect' level may be reasonably compared with the 'no effect' level among granite workers.

Two studies are reported in which workers were exposed to tridymite and cristobalite: the silica brick industry and diatomite industry.[15,16]

It appears that in the silica brick industry silicosis may occur after a short period of exposure. Examination of the data shows that there is no significant difference in the occurrence and extent of silicosis between green brick and burned brick workers. Silicosis occurred after exposure to a concentration of dust containing 75 to 90 per cent quartz. In terms of gravimetric estimation of respirable quartz this level may be comparable to that found in the granite industry, though probably somewhat lower.

In the diatomite industry a small number of cases were found after dust control, despite the mandatory use of respirators at peak levels.

Cases of silicosis have been reported in Ontario where there was exposure to pure silica flour.[19] In four plants an average dust concentration was given in

mppcf and related to a gravimetric measurement of respirable quartz. The lowest plant average was given as 0.21 mg/m^3, and this has been used in Table I as the lowest measurement at which an effect was observed. A safe level was not determined, but obviously it is lower than 0.21 mg/m^3.

Conclusion

In one study of granite workers[2] no silicosis was found when the average exposure of a small number of men (fewer than 32) was at a level of dust estimated to be the equivalent of 0.12 mg/m^3 respirable quartz. The time from first exposure to the chest x-ray examination appears to have been at least 12 years.

In another study[4] there were two groups of men without silicosis: a small number of men (11) exposed to a level of dust equivalent to 0.12 to 0.6 mg/m^3 respirable quartz for over 20 years and a larger group (107) exposed to a level of dust equivalent to less than 0.06 mg/m^3 respirable quartz for over 20 years. A silicotic effect was seen at a level of 0.4 mg/m^3 quartz.

In pottery workers,[14] however, cases of silicosis were observed at concentrations equivalent to 0.08 mg/m^3 respirable quartz, after lengthy employment, and in silica brick workers at levels equivalent to 0.05 to 0.1 mg/m^3 respirable quartz for varying time periods.

For workers with silica flour, cases of silicosis were seen at an estimated average dust concentration of 0.21 mg/m^3 or lower.

Acknowledgement

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Requests for reprints should be addressed to:
Dr. Joan C. McEwan
Special Studies and Services Branch
Ministry of Labour
8th Floor, 400 University Avenue
Toronto, Ontario M7A 1T7

Fig. I **Silicosis in Granite Cutters & Years of Exposure (Ref. 4).**

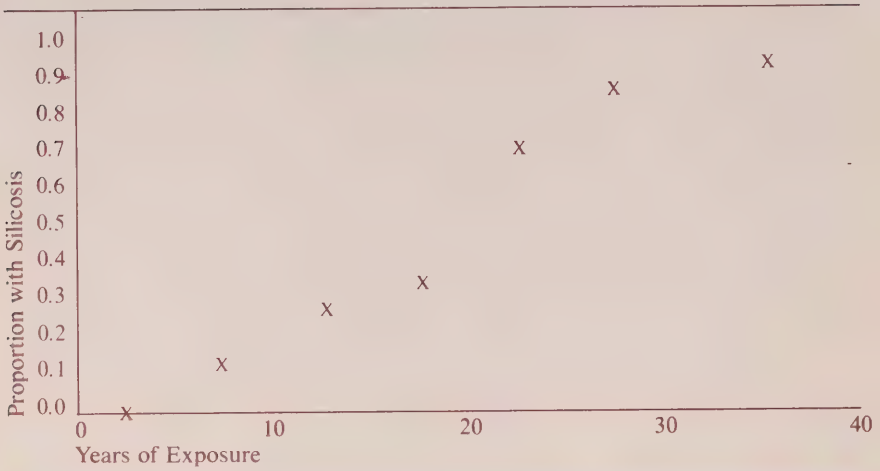


Fig. II **Silicosis among 'Others' in Granite Industry (Ref. 4)**

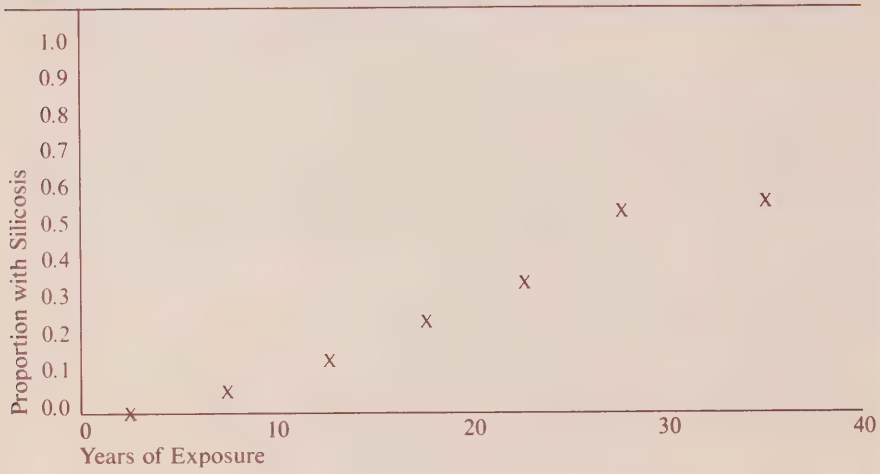


Fig. III **Silicosis in Underground Metal Miners (Ref. 10)**

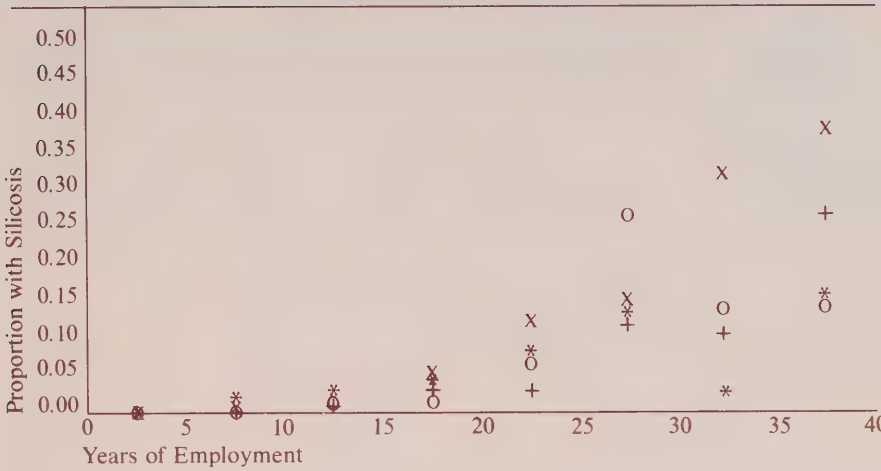


Fig. IV **Silicosis in Foundrymen (Ref. 11)**

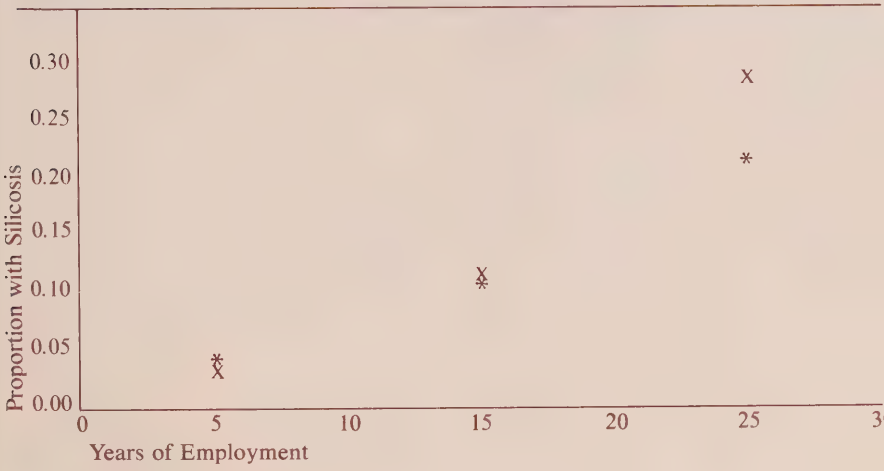
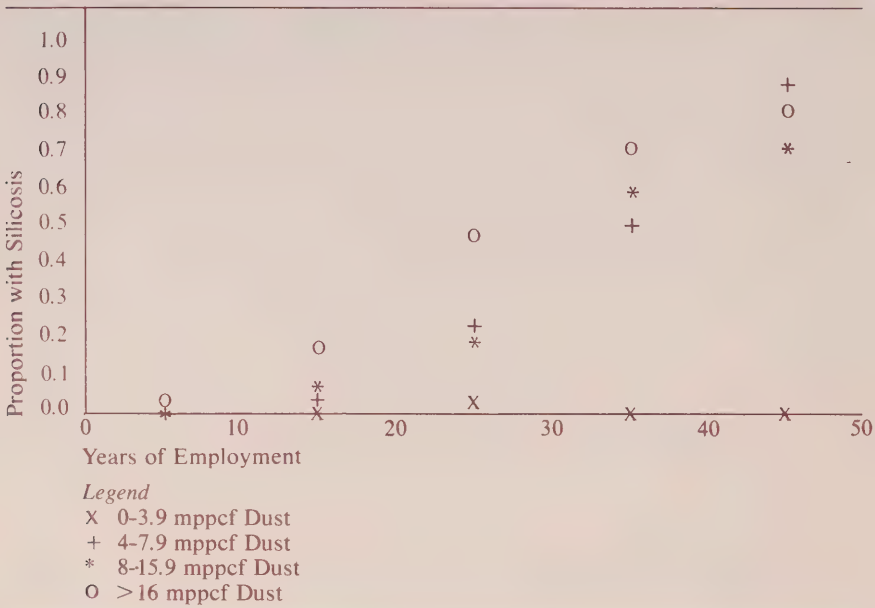


Fig. V **Silicosis in Pottery Workers (Ref. 14)**



Legend

x 0-3.9 mppcf Dust
\+ 4-7.9 mppcf Dust
* 8-15.9 mppcf Dust
o >16 mppcf Dust

Fig. VI **Silicosis in Silica Brick Workers (Ref. 15)**

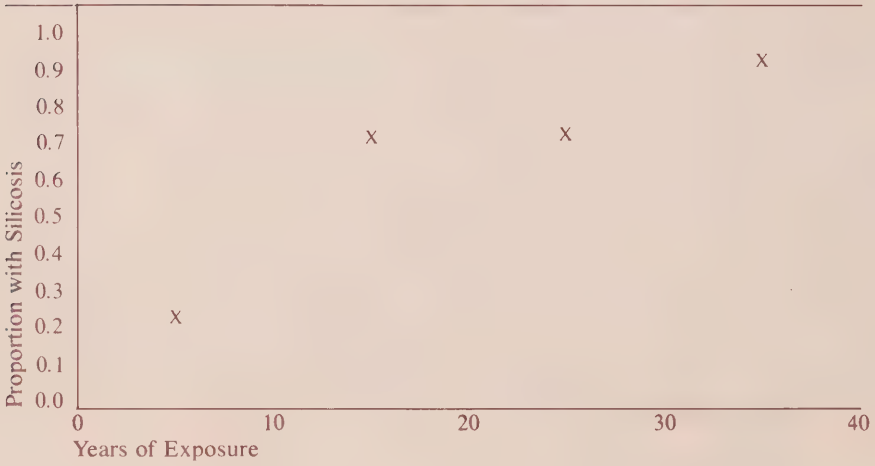


TABLE 1 **Levels of Respirable Silica in Selected Studies**

Study	Level of dust at which no effect was observed.	Level of dust at which silicosis was indicated.	mg/m³ Respirable Silica	
			No effect level	Lowest effect level
Granite Workers[2] (Russell)	6 mppcf. In fewer than 32 men, no effect was observed. Time interval from first exposure was at least 12 years.	At 20 mppcf, a harmful effect was questionable. Slight progression in silicosis in men who worked 10 to 19 years.	0.12[a]	0.4[a]
	< 12 mppcf: 11 men employed between 20 and 26 years as granite cutters showed no effect.		<0.12[b]	
Granite Workers[4] (Ashe and Bergstrom)	< 6 mppcf: 107 other granite workers employed between 20 and 26 years showed no effect.	~ 20 mppcf: 36 out of 66 men (55%) exposed for 30 years developed silicosis.	<0.06[b]	~0.4[a]
Pottery Workers[14] (Flinn)		< 4 mppcf: one silicotic among 223 men employed between 10 and 19 years, one silicotic among 65 men employed between 20 and 29 years, no cases in 29 men exposed for more than 30 years.		<0.08[c]
Silica Brick[15] (Fulton)	No silicosis found when average exposure was less than 2 mppcf.	Average exposure between 2 and 4 mppcf: 14 silicotics found among 65 men.	<0.05[d]	0.05 to 0.1[d]
Silica Flour[19] (Nelson)		1.9 mppcf: 3 silicotics found among men employed 6 to 16 years.		0.21[e]

Notes: [a] 10 mppcf dust = 0.2 mg/m³ respirable silica before dust control. (Ref. 22)
[b] 10 mppcf dust = 0.1 mg/m³ respirable silica after dust control. (Ref. 5)
[c] 1 mppcf silica = 0.1 mg/m³ total mass; assumed all particles are respirable and contain 20% free silica. (Ref. 24)
[d] 3 mppcf silica = 0.1 mg/m³ respirable silica; assumed 80% of particles are free silica. (Ref. 24)
[e] 1 mppcf silica = 0.11 mg/m³ respirable silica. (Ref. 19)

Dust concentrations in granite industry abstracted from Ref. 3 and 23 are attached as Table 2.

TABLE 2 (i) **Plants Equipped with Complete Dust Control**

	Dust Counts in Millions/Cu.Ft.		
	Min-imum	Max-imum	Av-erage
Pneumatic hand tool	4.5	29.0	12.5
Surface cutter, inside	5.3	45.0	15.1
Hand point	7.3	15.2	8.5
Carvers & Letterers	8.5	18.2	10.1
Tool grinders	3.0	9.9	8.1
General plant air	2.7	9.1	5.7
Polishers (wet)	4.6	12.3	8.2
Sandblasters	3.6	23.2	8.0
Sawyers (wet)	2.9	8.7	7.8

Source: Urban, E.C.J., Ventilation in the granite industry. J. Industr. Hyg. Tox. 21, 57, 1939.

TABLE 2 (ii) **Dust Counts in Granite Sheds by Occupation – 1955**

Occupation	Number of samples	Dust count (mppcf)*			
		Maximum	Minimum	Average	Median
Pneumatic hand tool operators	25	12.0	0.3	3.0	2.2
Carvers	12	11.0	.1	4.5	2.8
Surfacing machine operators	18	14.0	.1	3.3	2.2
Lathe operators	2	8.7	5.7	7.2	
Stonecutters using hammer or sledge:					
Exhaust used	7	2.9	.8	1.8	2.2
Exhaust not used	29	21.0	.6	8.8	6.2
Sandblast operators:					
Sandblasting	13	5.4	.2	2.1	2.5
Rubber cutting	7	1.4	.2	.8	.9
Polishers:					
All but final polish	19	9.8	0.4	4.3	3.5
Final polish only	6	59.0	4.7	22.0	13.1
Wire sawyers	11	7.4	.9	2.4	1.5
Cutting wheel operators	11	34.0	.3	5.3	1.5
Contour and grinding wheel operators:					
Wet	8	22.0	.8	6.9	2.3
Dry grinding	2	3.2	.4	1.8	
General plant air	53	22.0	.2	3.0	2.2

* Million particles per cubic foot of air

Source: (3) Hosey, A.D., Trasko, V.M., and M.B. Ashe, Control of Silicosis in Vermont Granite Industry Progress Report. U.S. Dept. Health, Education and Welfare. P.H.S. Publication 537, 1957

Radiological Classification of Silicosis in Studies Cited

1. *Granite Workers*
In the report by Russell[2] in 1941, chest x-rays were classified as:
a) Negative
b) More fibrosis than normal
c) Early silicosis
d) Moderate silicosis
e) Advanced silicosis
The classification used in the report by Ashe and Bergstrom,[14] is not stated. Theriault and co-workers[8] used the UICC (Cincinnati Classification of the Radiographic appearances of pneumoconiosis (1970).

2. *Metal Mining in the U.S.*[10]
Chest x-ray reports read in accordance with the International Classification of Radiographs of the Pneumoconiosis (I.L.O., Geneva, 1958) with minor modifications. The four major groups were:
a) Negative films or no pneumoconiosis
b) Suspect films – "Suspect" doubtful or "borderline" silicosis*
c) Small opacities including categories 1, 2 and 3 – simple silicosis*
d) Large opacities including complicated silicosis*
*Term used instead of pneumoconiosis for purposes of this study.

3. *Foundry Workers*[11]
Chest x-rays interpreted in the same way as for pottery workers.

4. *Pottery Workers*[14]
In workers considered to have silicosis, chest x-ray changes were described as Stages I, II, or III. The concensus at that time was to consider moderate exaggeration of linear markings, though possibly indicative of early silicotic changes, as non-specific and the diagnosis of silicosis was reserved for fine nodulation obliterating these markings (also depending on history, signs and symptoms).

5. *Silica Brick Workers*
Films were interpreted as:
Stage 1 silicosis: A diffuse ground glass appearance with or without obliteration of linear markings.
Stage 2: Disseminated nodules up to 1 mm diameter with or without emphysema.

Stage 3: Coalescent nodules and conglomerate shadows with accompanying emphysema.

6. *Diatomite Workers*[16]
A panel of three radiologists agreed that changes fell into two categories, one showing fine linear or minute nodular-appearing shadows and the other similar shadows accompanied by more extensive confluent opacities. It was noted that in all films, nodules were small and were never so dense or discrete as those characteristic of quartz silicosis. Grading was into LN_1, LN_2, LN_3, C_1, C_2, C_3, and C_4.

Grade LN_1 implied 'doubtful evidence of pneumoconiosis'. Grades LN_2 and LN_3 alone or in combination with C grades implied 'definite evidence of pneumoconiosis'.

7. *Ontario*[21]
Six-point numerical system,
'5' rating denoting "generalized arborization with partial mottling" is considered to be the first definite sign of silicosis.

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Murray Finkelstein
PhD, MD

The Importance of Worker Compliance in The Use of Hearing Protectors

Summary

In order to provide effective noise reduction, hearing protectors must be worn virtually 100 per cent of the time. Achievement of this level of compliance requires comfortable devices and a well-informed work force.

British researchers have shown that the effects of noise upon a population of workers may be described statistically by the use of the so-called Equal-Energy Principle.[1,2] According to this principle, hearing loss is related to the quantity of noise energy reaching the ear, and the quantity of noise energy is determined by the combination of noise level and duration of exposure. The principle states that equal amounts of noise energy produce equal amounts of hearing damage, no matter what combination of noise level and duration they are composed of; thus exposure to a certain noise level for four hours will have the same statistical effect as exposure to a noise level half as great for eight hours, or one twice as great for two hours. This is the reason why tables of noise levels and permitted exposure times appear in noise regulations.

In order to understand the implications of this principle for hearing protection, one must first understand the way in which noise levels are added together. This procedure is complicated by the fact that noise levels are described not on the linear scale of everyday experience, but on the *logarithmic* scale, in which points an equal distance apart are separated not by an equal additive factor, but by an equal multiplicative factor. Thus, on the linear scale, the numbers 5, 15, 25, and 35 are an equal distance apart, separated by the additive distance of 10 units; on the logarithmic scale, the numbers 5, 50, 500, and 5000 are an equal distance apart, separated by the multiplicative factor of 10.

Noise levels are measured on the logarithmic decibel (dB) scale. In mathematical terms, the noise level is related to the sound pressure, p, and sound intensity, I, as follows:

$$\text{Noise Level} = 10 \log p^2 = 10 \log I \text{ dB}$$

and thus the noise level of a sound which is twice as intense as another is 3 dB higher, that is

$$\begin{aligned}\text{Noise Level} = 10 \log 2\,I &= 10 \log I + 10 \log 2 \\ &= 10 \log I + 3 \text{ dB}\end{aligned}$$

Thus by doubling the intensity of noise, the noise level increases by 3 dB, no matter what the level of the original sound. By way of example, if a fan generates a noise of 90 dB and a jet engine generates a noise of 125 dB, then two fans will produce a noise of 93 dB and two jets will generate a noise level of 128 dB, a surprising result for those of us used to thinking on the linear scale. Conversely, if an airline worker standing between two jets puts on a pair of earmuffs which reduce the sound intensity by half, the noise level affecting his hearing will be reduced from 128 to 125 dB.

Consider now a pair of hearing protectors which provide 20 dB of protection; that is, they reduce the sound intensity by a factor of 100. What is the effective noise reduction if they are worn for only half a work shift? The worker will be exposed to unit intensity for half the shift, and to an intensity 100 times greater for half the shift. The time-weighted noise level is thus $N = 10 \log (\frac{1}{2} \times 100) = 17$ dB. Wearing protectors providing 20 dB of protection for only half the shift thus provides effective protection of only 3 dB, and the Equal-Energy Principle implies that this will produce the same damage as a reduction in environmental noise of 3 dB and the use of no protection at all. Thus if a worker employed in a workplace where noise levels have been measured at 105 dB is provided with hearing protectors rated at 20 dB and wears them for only half the shift, his effective noise exposure will be 102 dB. If he wears them for seven hours out of an eight-hout shift, his effective exposure will still be 96 dB rather than the 85 dB it would be if he wore them for the whole shift.

Table I outlines the amount of protection provided by a pair of protectors rated at 20 dB worn for varying lengths of time in an eight-hour shift. It can be seen that the amount of protection provided falls off *rapidly* with the length of time that the protectors are not worn. Not wearing the protectors for as short a time as five minutes reduces the effectiveness by 2 dB.

It is thus imperative that, in any workplace where the use of hearing protectors forms an integral part of the hearing protection program, compliance be excellent, otherwise most of the desired protection will be lost. This requires that the protectors be comfortable and not distressing to wear. An education program with periodic reinforcement must inform the workers

of the importance of proper compliance with the program. Earmuffs and plugs can provide protection, but they must be used properly by a well-informed work force.

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Table I

Protection Provided by Hearing Protectors Rated at 20 dB and Worn for Various Lengths of Time in an Eight-Hour Shift

Time Worn	Effective Protection
8 hours	20 dB
8 hours less 5 minutes	18.2 dB
8 hours less 10 minutes	16.8 dB
8 hours less 15 minutes	15 dB
8 hours less 30 minutes	12 dB
7 hours	9 dB
6 hours	6 dB
4 hours	3 dB

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Dr. Murray Finkelstein, Special Studies and Services Branch, Ministry of Labour, 8th Floor, 400 University Avenue, Toronto, Ontario. M7A 1T7

Douglas H. Harding
MD

Carcinogenesis – Interpreting Test Results*

Summary

A simplified version of carcinogenesis is presented which is intended to serve as a working model. It is also intended to make a distinction between risks arrived at by toxicological testing and those derived from epidemiological studies.

The second part deals with various new mutagenesis testing systems coming into style, and attempts to outline their advantages and disadvantages.

To begin with, I would like to describe one of the processes by which liver cells metabolize or break down organic chemicals in a very simplified schematic fashion. It should be borne in mind that this process is a normal function of the cell.

Toxicity

When a foreign substance is taken in by the body, enzymes in the liver cells act to hydroxylate the compound, and in that form it can be conjugated and excreted. (Figure I)

The cell contains a system of enzymes to carry out this function. These have been referred to by a variety of names, such as drug metabolizing enzymes, mixed function oxidases, or P 450, and are located in the cell on the smooth endoplasmic reticulum (SER), which is a series of smooth membranes within the cytoplasm. Biochemists who break down the cell to study its parts refer to the enzyme system by the term "microsomal enzymes", named after the microsomal layer seen following ultra-centrifugation of the emulsified cells.

It has been observed that when a substance such as a drug is administered to an animal at a dose greater than the liver cell can handle, the enzyme system expands in order to detoxify the drug more efficiently. This effect is referred to as enzyme induction. Generally accompanying the induction of drug metabolizing enzymes, there is proliferation of the SER which can be observed on the electron microscope. After the foreign organic material has been detoxified, the enzymes return to normal levels, and the SER decreases in size. All of this activity can be considered as a normal cellular function.

In studying the mechanism whereby certain chemical substances cause cancer, it seems that the metabolic pathway leading to conjugation and the enzymes naturally involved may be related to the carcinogenic action of that substance.

The process leading to conjugation is represented in Figure II.

However, between the PCB and the hydroxylated form there exists a very reactive intermediate referred

* Given at the Second Ontario Crop Protection Conference, University of Guelph, November 21-22, 1979.

to as an epoxide or arene oxide. Epoxide refers to aliphatic molecules while arene oxide refers to aromatic compounds. The term epoxide seems to be used loosely. (Figure III).

Most of the epoxide formed will be converted to the hydroxyl form, conjugated and excreted. A small percentage, nevertheless, will react with macromolecules within the cytoplasm. Most of these reactions will be of no great importance, or will form a compound having acute toxic effects on the cell. Finally, a small percentage will react with the DNA of the chromosomes and initiate the conversion of the cell to a malignant cell. (Figure IV). The element of risk can be seen in these percentages. The risk of developing cancer can be seen as a continuum, decreasing with decreasing doses, but never reaching zero.

The epoxide form of many different chemicals may be carcinogenic and this chemical structure can be thought of as a common denominator found in many carcinogenic substances. To qualify as a carcinogen, in addition to the formation of the epoxide or arene oxide, in some cases the molecule must also be coplanar or flat like a disc.

The cell contains a healing system of enzymes whose function is to repair the damaged DNA, but a percentage of the damage escapes repair. Once a cell divides, the damage to the chromosome becomes locked in and the cell is now a cancer cell. All of the above reactions can occur within minutes of the PCB entering the cell.

The reaction with the DNA is as follows: The epoxide group combines with one of the bases making up the DNA helix. This swings in the rest of the molecule to fit between the bases – a process referred to as intercalation. (Figure V). The intercalation is the reason why the molecule must be coplanar in order to fit between the bases. The intercalated molecule now spreads the bases apart, resulting in the insertion of another base referred to as a frame shift.

The resulting shift results in a gene having a new sequence of bases which may express itself as one of the unholy trinity of mutagenesis, carcinogenesis or teratogenesis.

The process of carcinogenesis is depicted in Figure VI.

The question now apparent in this process is why, after the cell becomes a cancer cell, does it not become a growth? What is this latent period that people talk about lasting for 20 to 30 years? One explanation is that the body has an immune system capable of

suppressing the growth of the malignant cells until age sets in when the immune system begins to slowly deteriorate and one of the malignant cells begins to proliferate.

Animal studies have shown that cells can be altered to malignant cells in four weeks and that the number of such cells remain stable after 50 weeks, indicating that the body is not capable of eliminating malignant cells.

The immune system must be involved, since destruction of the immune system in animals results in an earlier development of cancer in those animals as compared to controls.

Risk

From discussion on the toxicology and from animal studies and epidemiological investigations the concept of risk as a continuum has been developed in relation to long term effects such as carcinogenesis. In order to provide a conservative margin of protection against long term effects, the dose-response curve is extrapolated back through zero, indicating that no threshold dose-response curve exists, and also indicating that there is no safe exposure level. Each exposure will carry some degree of risk but the risk increases with increasing exposure.

If risk is a continuum, then some point must be arbitrarily chosen as the level of acceptable risk. The question then must be asked, "Who sets the level of acceptance risk?" Industry would have us believe that the acceptable risk is the price we must pay for the benefits and rewards of living in our modern society. However, industry blurs the distinction between demands and needs. We must all cooperate to assess the risk, including industry, government, unions and the public, but most emphasis should be placed on the public by informing it and allowing it to define the word "need", as opposed to demand, before accepting the related risk. It is unthinkable to me that a small group of people should decide what risk is acceptable and then impose it upon society. People have the right in matters relating to human and environmental health to have access to information and the right to have that information interpreted by the experts of their choice.

Mutagen/Carcinogen Short-Term Tests

Some of the short-term mutagenic assays are briefly described below.

The Ames Test

This test has been the most extensively applied short-term assay and is meeting with general acceptance. It has been recently reviewed for this journal by Ronald House[4].

Forward and Reverse Mutations

Mutations can be either forward or reverse. The Ames test uses reverse mutation in which a prior mutation is caused to revert to normal by a mutagenic substance. This means that the mutagen cannot just react with the DNA at any given point to produce its effect but must react at that specific point where the prior mutation lies. A forward mutation is more general and consists of the agent causing a mutation anywhere in the DNA, and resulting in a viable mutated colony. It is felt that forward mutations would be better than the reverse mutation, but in practice both systems are equally sensitive. The reason for favoring a forward mutation is the overall ability to detect a mutagen. There are four ways to produce a mutation: (1) base pair substitution or destruction, (2) frame shift, (3) chain termination and (4) large deletions. If the mutagen is to be detected in a reverse mutation, the type of mutation which that mutagen induces would have to be present in the bacteria, or else the mutagen would go undetected. All possibilities, known or unknown, are covered in the forward mutation. The Ames test therefore uses several different tester strains of Salmonella containing the different types of mutations, hopefully to detect any type of mutagen.

Newer Short-Term Mutation Tests

Many other short-term testing systems are being developed but are not yet widespread in their application. Interpretation of their results suffers from lack of standardization, lack of well-trained people to carry the tests out and lack of reproducible results between laboratories.

Several tests are gaining favor and are described briefly below. The need for these tests arises from the problems of false positives and negatives. The best

way to assess the mutagenic potential of a substance is by applying a battery of tests presently resulting in about 99 per cent efficiency.

Host-Mediated Assay

The substance is first administered to a mouse for about five days to take advantage of the complete metabolic activation. The bacteria are then injected intraperitoneally for three hours, removed and cultured to determine the number of mutants.

Mammalian Cell Mutation System

This is an interesting system which incorporated the idea of the Ames test into a mammalian cell. It is referred to as the CHO/HGPRT system and is based on the following discovery. CHO refers to Chinese Hamster Ovarian cells grown in culture. The X chromosome in these cells contains the locus for the HGPRT enzyme (Hypoxanthine-guanine phosphoribosyl transferase). If the enzyme were present, it would metabolize a purine analogue (6-thioguanine) to produce a toxic metabolite and kill itself. If a mutagen were added to the cell culture, a forward mutation would occur and the cell could lose the HGPRT gene and consequently develop resistance to the purine analogue in the culture. The number of resulting colonies could then be counted and scored against the various mutagens.

This test system can be modified by the addition of microsomal enzymes for metabolic activation as in the Ames test. It is also possible to perform the assay using the host-mediated system.

Transformation Systems

This is a group of very important assays and are considered essential in a battery of tests along with the Ames test. The Ames test plus a transformation test can detect 99 per cent of the known mutagens.

One of the factors influencing the multiplication of cells in a tissue is contact inhibition. A cut in the skin releases the contact pressure and the cells begin to grow until the pressure is reestablished and the cut is healed. Cells grown in tissue culture show this phenomenon and they tend to form a monolayer over the surface of the container, although they pile up only to a very limited extent. When the cells are treated with a carcinogen, however, they become transformed, lose their contact inhibition and will develop into colonies

with extensive piling up. The cells in the colony are fusiform in shape and form a random criss-cross pattern. Reinjected into an animal, the cells are tumorigenic.

Many cell cultures from established cell lines and from embryonic tissues have been used for these studies. However, no human cell line has yet been developed.

There are two interesting variations:

1. *A transplacental assay* in which the mutagen is administered to pregnant hamsters. The embryos are later taken and embryo cell cultures prepared. Transformation in these cultures indicate that the test substance or its metabolites crossed the placenta. The test makes use of the whole animal's metabolic activation and detoxification system, and as well can be used with multiple test substances to measure synergistic effects.

2. *A system combining virus and chemicals* The cultured mammalian cells are exposed to both virus and a test substance. The theory is that the virus is better able to transform the cells when the DNA has been damaged by the mutagen. The mutagenic effect would otherwise not have been apparent.

Drosophila

The fruit fly is the most genetically well understood whole animal and has been used extensively for all types of mutagenic testing. The disadvantage of its use is in the extrapolation of findings to man.

The house mouse ranks second to Drosophila in genetic characterization. The extrapolation of experimental results to man is more acceptable. Mutagenicity in the mouse is divided into two categories:

1. Somatic cell damage
2. Germ cell damage

Under somatic cell assays there are three test procedures which I will describe briefly.

1. *Micronuleus test*

This consists of the microscopic examination of the bone marrow for small nuclear fragments in red blood cells as an indication of treatment-induced genetic damage. A serious problem in this test is the assumption that the chromosomal fragments are due to direct

genetic damage. The micronuclei could have resulted from a toxicant effect of the test substance on the cell.

2. *Cytogenetics*
This is the usual examination of cultured cells for chromosomal aberrations such as breaks, gaps, deletions, translocation and ploidy, and any increase would be considered indicative of mutagenic activity. Caution is needed in interpreting results since the cause of the breaks may not represent single gene mutations, and because the effects seen in somatic cells may not parallel effects in the germ cells. Also, as above, the breaks may be due to toxic effects and not mutagenic effects.

3. *Sister Chromatid Exchanges*
A method of incorporating identifying substances into the chromatids during their replication allows the identification of reciprocal exchanges of DNA between the chromatids. The disadvantage to this test is that a mutagen which acts in some fashion other than the induction of DNA exchanges would be missed.

Germ Cell Damage

There are two tests in this group that I will outline, including the important

1. *Dominant Lethal Assay*
If the germ cells are damaged by a mutagen to a significant degree, the embryos conceived will die *in utero* at various stages of development. The procedure involves exposing the male to the test substance, followed by mating and evaluation of the number of dead and living embryos. The test is inexpensive, quick and widely used. The mutations involved are most likely to be chromosomal aberrations rather than single gene mutations. A disadvantage in the test is its insensitivity, due to a high and variable incidence of spontaneous lethals. A criticism of the test has been made by referring to it as an irrelevant test since the embryos die and pose no genetic hazard to future generations. The defence to this criticism is that fetal death or abortions are not irrelevant to humans and must be considered in evaluating risks to humans.

2. *Sperm Morphology*
This is a straightforward assay of sperm morphology in treated and untreated animals. In spite of its simplicity, it correlates well with the Ames test.

Application and Interpretation

I would next like to say a few words about the application of these short-term tests and their interpretation. In the preceding descriptions, I have indicated that there are shortcomings in all of the tests and that no one test can be relied upon to detect all the carcinogens and clear all the non-carcinogens. Two systems of testing are recommended (a) *the Battery System* and (b) *the Tier System*. The tier system consists of screening the test chemicals initially with an easily performed inexpensive test followed by more extensive testing of positive chemicals. The battery system subjects the chemical to several tests for comparative purposes. This allows one test to cover for the deficiencies in another test. The battery system is considered the better because in the tier system a negative finding in the first screen could falsely eliminate a potential mutagen from further consideration.

The interpretation of test results is hampered because of the difficulty in relating the dose administered to a culture system to the risk that would be experienced by a human or other mammal with a complex metabolic system including detoxification, DNA repair systems, and immunological defences. The short-term tests using whole animals are not yet fully validated and standardized. They generally exist only in the originators' laboratory where they give excellent results with trained personnel, but have yet to be developed for general use.

What the screening tests can do is identify possible mutagens and rank them. Those with high mutagenic potential should then be studied in long-term animal experiments. Of course the long-term animal studies themselves fail because of their expense and the few animals that can be studied per test group. Any attempt to increase the size of the test groups in animal studies quickly increases the cost and time required.

My final word of caution is that carcinogenesis is a crude end point. A more subtle toxic effect from mutagens could be their effect on the mutation rate of the human gene pool with serious consequences for future generations. It can be easily observed that cigarette smoking kills about 70,000 Americans per year but it is not known if the children of smoking parents carry an increased number of recessive mutations.

Requests for reprints should be addressed to: Dr. D.H. Harding, Sr. Medical Consultant, Special Studies and Services Branch, Ontario Ministry of Labour, 8th Floor, 400 University Avenue, Toronto, Ontario M7A 1T7.

1. Scott D, Bridges B, and Sobels F. *Progress in Genetic Toxicology*. New York: Elsevier/North Holland, 1977.

2. Flamm WG and Mehlman M. *Advances in Modern Toxicology, Mutagenesis*. New York: John Wiley and Sons 1978: Vol. 5.

3. Butterworth B. *Strategies for Short Term Testing for Mutagens/Carcinogens*. Florida: CRC Press, 1979.

4. House R. *The Ames Test – An Initial Appraisal. Occup. Health in Ont. 1980; 1 (2): 2-11.*

Fig. I **Conjugation Model**

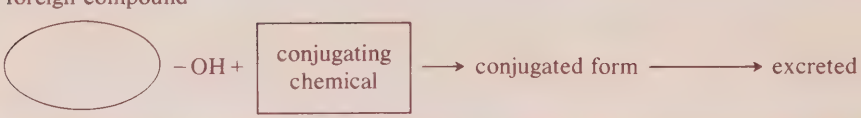


Fig. II **Hydroxylation of PCB**

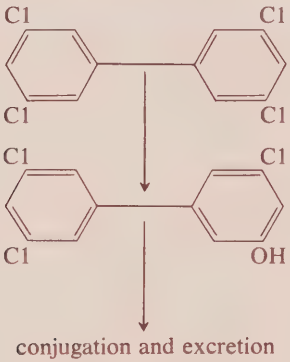


Fig. III **Intermediate Step in PCB Hydroxylation**

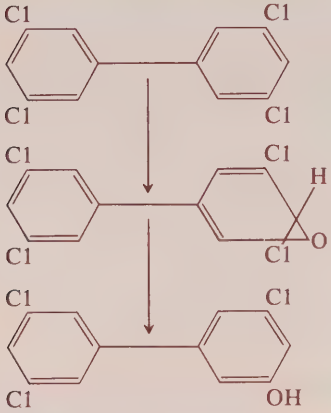


Fig. IV **Metabolic Model of an Arene Oxide Showing The Toxicological Assessment of Risk**

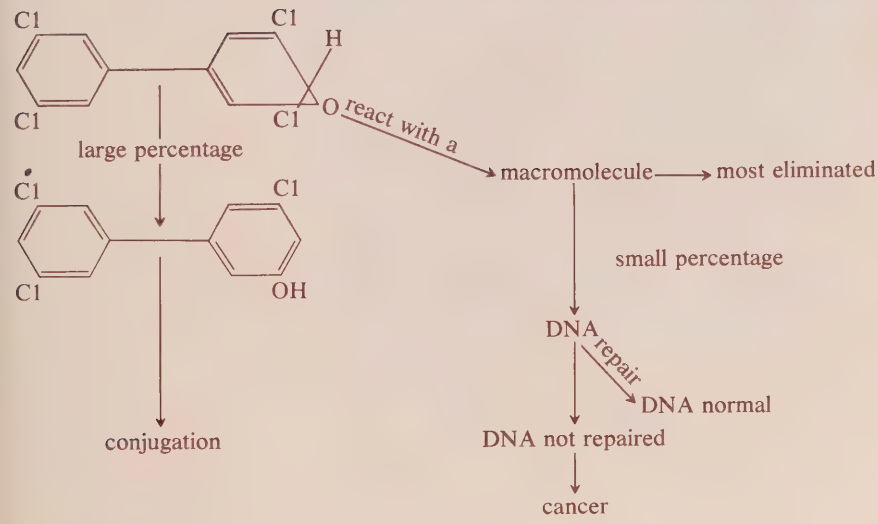
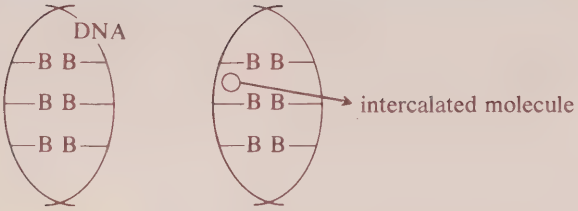


Fig. V **Illustration of Intercalation**



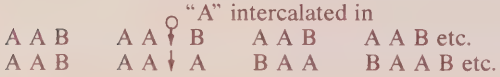
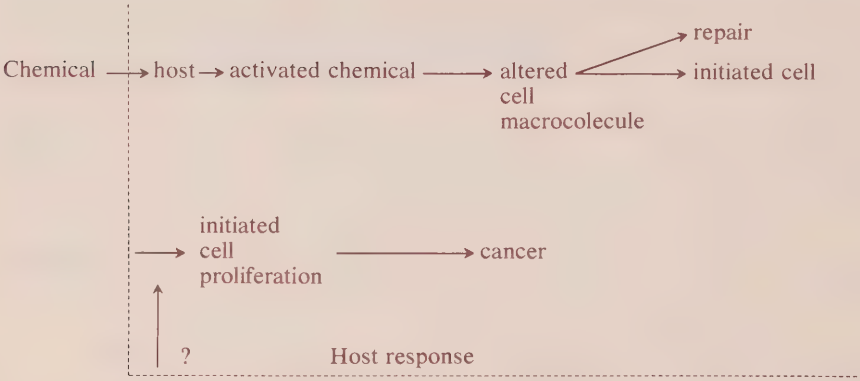


Fig. VI **Steps in The Development of a Neoplasm in a Host**



Occupational Health Notes:
R.E.M. Lees
Printed in Canada, 1980
Distributor: Avitalis, Box 936, Kingston, Ont.
Price: $10

Book Review

This little book intends to be a brief guide to general practitioners who work part-time in industry, the occupational health nurse and the medical student interested in occupational health. It has no intention of replacing "large" textbooks of occupational medicine.

With this in mind it includes a definition of occupational health and a description of occupational health services – plant inspections, periodic preventive examinations of exposed workers, and occupational hygiene – emphasises the importance of an overall health maintenance program and, finally, discusses compensation.

The remaining 83 of the 104 pages cover hazards in the working environment. It is a pity that the author did not include a short discussion of general and personal protective devices. Attention is drawn to the difference between absolute and effective toxicity but one or two additional examples would have been helpful to explain this important issue more thoroughly.

The individual chapters could be better edited. Some important hazards are not mentioned. For example, no reference is made to damage to the eye by hydroquinone when phenols are discussed, nor is reference made to pneumonitis due to excessive exposure to manganese, though damage to the respiratory tract due to exposure to mercury is described.

It also fails to note that the action of irritant gases on the respiratory tract depends on their solubility, e.g., the soluble sulfur dioxide damages mainly the upper respiratory tract, whereas the less soluble nitrogen dioxide, or phosgene gases, will damage the lungs without necessarily causing symptoms of irritation of the upper respiratory tract. The tables are very instructive. However, "normal values" of concentration should be called 'values in unexposed individuals.' A person exposed to lead might have a concentration of

60 micrograms/100 ml of blood and still be normal, i.e., without any physiological signs of lead exposure. Some statements, such as "the bones become softened in fluorosis" are misleading.

On the whole the book could be very useful but it must be read circumspectly, pending a new edition. The *Encyclopedia of Occupational Health and Safety, Internation Labour Office*, Geneva 1975. should be added to the list of suggested books. The corrigenda list is incomplete (i.e., 'lead' blood: less than 30 micrograms/l – should read 30 micrograms/100 ml.)

J. Budlovsky

News and Notes

International Symposium on Prevention of Occupational Cancer

The International Symposium on Prevention of Occupational Cancer is organized by the Institute of Occupational Health, Helsinki, Finland, in collaboration with the International Labour Office (Geneva), World Health Organization (Geneva), and International Agency for Research on Cancer (Lyon).

The symposium will be held at Finlandia Hall, Helsinki, April 21-24, 1981.

Agenda

Theme I	Current concepts in occupational carcinogenesis.
Theme II	Epidemiology of occupational cancer.
Theme III	Methodology for occupational cancer risk evaluation.
Theme IV	Prevention and control of occupational cancer risk.

Working languages: English and French with simultaneous interpretation.

Further information may be obtained from:
International Symposium on Prevention of Occupational Cancer,
Institute of Occupational Health,
Haartmaninkatu 1,
SF-00290 *HELSINKI* 29 (FINLAND)

Tel. (90) 413.622

Coming Events

November 18, 1980	American Industrial Hygiene Association, Ontario Section. Seminar – Asbestos. *Toronto.*
March 26-27, 1981	Society of Occupational Medicine. Spring meeting. *London, England.*
April 7-10, 1981	British Occupational Hygiene Society Annual Conference. *Nottingham, England.*
April 26-May 1, 1981	American Occupational Health Conference. *Atlanta, Georgia.*
June 13-16, 1981	Annual Provincial Meeting. Society of Occupational Medicine. *Durham, England.*

Ontario Ministry of Labour

Occupational Health and Safety Division

Occupational Health Branch

400 University Ave.
Toronto, Ontario
M7A 1T7

Telephone:
(416) 965-3610

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